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# Impact of Compressional Force, Croscarmellose Sodium, and Microcrystalline Cellulose on Black Pepper Extract Tablet Properties Based on Design of Experiments Approach

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**Abstract:** This study aimed to prepare tablets of black pepper extract using the Design of Experiments (DOE) approach. The levels of three factors—compressional force, croscarmellose sodium (CCS), and microcrystalline cellulose (MCC)—were screened using the one-factor-at-a-time technique, followed by the DOE utilizing the Box–Behnken design. The respective variations for each factor were as follows: compressional force (1500–2500 psi), CCS (1–3%), and MCC (32–42%). The results indicated that compressional force significantly decreased tablet thickness and friability, while increasing hardness and prolonging disintegration time. CCS significantly shortened disintegration time but did not affect tablet thickness, hardness, and friability. MCC, on the other hand, significantly increased tablet thickness and hardness, while significantly decreasing friability. Furthermore, the study observed interactions among factors and quadratic effects of each factor, which significantly influenced tablet properties. The optimal tablet formulation consisted of 2.2% CCS, 37% MCC, and a compressional force of 2000 psi. These tablets had a weight of 198.39 ± 0.49 mg, a diameter of 9.67 ± 0.01 mm, a thickness of 1.98 ± 0.02 mm, a hardness of 7.36 ± 0.24 kP, a friability of 0.11 ± 0.02%, and a disintegration time of 5.59 ± 0.39 min. The actual values obtained using the optimal conditions closely matched the predicted values, with a low percent error (less than 5%). In conclusion, the application of the DOE approach successfully developed tablets of black pepper extract, which can be utilized as food supplement products.

**Keywords:** Box-Behnken design; direct compression; one factor at a time; piperine; response surface methodology



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## 1. Introduction

Black pepper (*Piper nigrum* L., Piperaceae) is widely known as the "king of spices" and has been extensively studied for its various biological activities. It exhibits numerous pharmacological effects, including antimicrobial, antioxidant, anticancer, neuroprotective, hypoglycemic, anticonvulsant, analgesic, hypolipidemic, and anti-inflammatory properties [1]. The most commonly reported traditional uses of black pepper for medicinal purposes are related to menstrual disorders, ear–nose–throat disorders, gastrointestinal disorders, skin diseases, and fever [1]. One of the major bioactive compounds in black pepper is piperine, which accounts for approximately 2–7.4% of its composition [2]. Piperine demonstrates a wide range of pharmacological effects, such as anti-aging, anti-allergic, anti-angiogenesis, antidiabetic, anti-inflammatory, antimicrobial, anti-obesity, antioxidant, antiproliferative, antitumor, cardioprotective, hepatoprotective, immunomodulatory, and neuroprotective

effects [2]. Among these, its anti-inflammatory effect has been well-documented. Piperine inhibits prostaglandin E2 and nitric oxide, reduces the expression and production of tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase, and cyclooxygenase-2, and inhibits lipopolysaccharide-mediated activation of nuclear factor-kappa B (NF-κB) and degradation of inhibitor-kappa B (IκB) proteins [3,4]. Piperine also possesses bioavailability-enhancing properties. It has been shown to increase the absorption of (-)-epigallocatechin-3-gallate, emodin, ginsenoside Rh2, puerarin, and other medicines in both in vitro and in vivo studies [5]. Clinical trials have documented the use of piperine as a bioenhancer for curcuminoids (especially curcumin), coenzyme Q10, β-carotene, cannabinoids tetrahydrocannabinol and cannabidiol, resveratrol, and several other medicines [5,6]. The proposed mechanisms for its bioenhancing effects include modulation of local mucosal tissue, thermogenic activity, inhibition of elimination (gastrointestinal transit and gastric emptying), inhibition of metabolism (cytochrome P450 and hepatic and intestinal glucuronidation), and inhibition of efflux transporters (such as P-glycoprotein) [7]. However, it is important to note that piperine can affect the pharmacokinetics of co-administered medicines, which may have either therapeutically advantageous or adverse effects. Depending on the specific treatment circumstances, piperine can either inhibit or stimulate the functioning of metabolic enzymes and transporters [8].

In terms of solid oral dosage forms, tablets have emerged as the most commonly used form. Among the various methods available for tablet manufacturing, direct compression is the preferred approach. When compared to wet or dry granulation methods, direct compression offers several advantages. These include reduced machinery, energy, and space requirements, as well as decreased processing time. Additionally, direct compression minimizes the risks associated with microbiological growth, moisture deterioration, and degradation of thermal-sensitive compounds. This is achieved by reducing the number of operational processes, minimizing the potential for cross-contamination from operating procedures, and eliminating the use of water. Tablets produced through direct compression also tend to exhibit faster dissolution rates. However, for successful tablet production, it is crucial to have pharmaceutical excipients with desired properties, such as good flowability, compressibility, and compactability [9]. Various food supplement products have been developed in tablet form, including barberry fruit pulp tablets [10], rice bran tablets [11], and *Aronia melanocarpa* effervescent tablets [12]. However, to achieve the desired tablet properties, several factors that influence tablet characteristics must be optimized.

In an experiment and during the formulation development of a tablet, one or more process variables are intentionally modified to observe their impact on one or more response variables. The design of experiments (DOE) method is employed to efficiently plan and conduct experiments, yielding precise data that can be analyzed to generate reliable and unbiased results [13]. DOE, as a systematic approach, proves valuable in addressing challenges encountered in research, development, and manufacturing [14]. It serves multiple purposes, including comparison, variable screening, identification of transfer functions, system optimization, and robust design. Furthermore, DOE is widely utilized across various fields such as astronomy, biochemistry, computer sciences, engineering, genetics, medical sciences, physics, etc. [15].

The classic approach to experimentation relies on the trial-and-error method, which is unstructured, ineffective, and particularly problematic when lacking subject matter expertise. Another commonly used technique is the one-factor-at-a-time (OFAT) approach. With OFAT, one factor is modified, the response is measured, and then the process is repeated with a different factor. However, this strategy rarely uncovers the optimal set of conditions when multiple factors are involved. This is where DOE proves beneficial [16]. By employing DOE, significant time, money, and resource savings can be achieved compared to traditional trial-and-error and OFAT methods. Additionally, DOE enables the identification of factor interactions and the characterization of the response surface [17,18]. Moreover, a statistical model can be employed to anticipate the simultaneous impact of multiple factors [16].

Therefore, the objective of this study was to prepare tablets of black pepper extract using the DOE approach, with the intention of producing a food supplement that promotes health benefits. Furthermore, the Box–Behnken design was employed to elucidate the effects of compressional force, croscarmellose sodium (a tablet disintegrant), and microcrystalline cellulose (a tablet diluent and binder) on the properties of black pepper tablets.

## 2. Materials and Methods

### 2.1. Materials

Black pepper extract powder (piperine 10%) was purchased from AP Operations Co., Ltd., Sri Racha, Chon Buri, Thailand. Piperine (purity 98.78%) was purchased from Chengdu Biopurify Phytochemicals Ltd., Chengdu, Sichuan, China. Fumed silica was purchased from P.C. Drug Center, Khan Na Yao, Bangkok, Thailand. Magnesium stearate was purchased from Changzhou Kaide Imp. & Exp. Co., Ltd., Changzhou, Jiangsu, China. Croscarmellose sodium (CCS) was obtained as a gift from Onimax Co., Ltd., Yannawa, Bangkok, Thailand. Microcrystalline cellulose (Comprecel® M102, MCC) was purchased from Maxway Co., Ltd., Pravet, Bangkok, Thailand. Dibasic calcium phosphate was purchased from Krungthepchemi, Lat Phrao, Bangkok, Thailand. Methanol (HPLC grade) was purchased from Fisher Chemical, Leicestershire, Loughborough, UK. Ultrapure water was produced by Direct Q 3 UV system, Merck Ltd., Khlong Toei, Bangkok, Thailand.

### 2.2. Preparation of Black Pepper Extract Tablet and Screening of Level of the Factors Using the OFAT Technique

The ingredients used in the black pepper extract tablet formulation included black pepper extract powder as the active ingredient, fume silica as a glidant, magnesium stearate as a lubricant, CCS as a disintegrant, MCC as a diluent/binder, and dibasic calcium phosphate as a diluent. All the ingredients were sieved through a 40-mesh sieve, except for magnesium stearate, which was sieved through a 60-mesh sieve. For a prototype formulation of 10 g, 2.5 g of black pepper extract was mixed with 4.2 g of MCC for 3 min (Mixture I). A premix was prepared by mixing 3.1 g of dibasic calcium phosphate, 0.1 g of fumed silica, and 0.1 g of magnesium stearate for 1 min (Mixture II). Subsequently, Mixtures I and II were mixed for 3 min. The resulting powder mixture was then weighed at 200 mg, and a hydraulic press connected to a pressure gauge was utilized to compress it into a tablet.

The levels of three factors, namely, compressional force, CCS content, and MCC content, were screened using the OFAT technique. Each factor was varied across four levels: compressional force of 1000, 1500, 2000, and 2500 psi; CCS content of 0, 1, 2, and 4%; and MCC content of 27, 32, 37, and 42%. In the case of CCS addition, it was premixed in Mixture II. The resulting tablets were evaluated in terms of five parameters, including weight and weight variation, thickness and diameter, hardness, friability, and disintegration time (DT). However, only tablet thickness, hardness, friability, and DT were compared.

### 2.3. Box-Behnken Design for Optimization of Black Pepper Extract Tablet

Based on the screening of factors' levels using the OFAT technique, three levels of each factor were included in the Box–Behnken design (Table 1). They varied as 1500–2500 psi, 1–3%, and 32–42%, respectively. So, 17 conditions composed of 12 axial points and 5 center points were obtained.

The properties of black pepper extract tablets obtained from 17 different conditions were compared to the predicted values, and the percentage errors were reported. Three-dimensional (3D) response surfaces for tablet thickness, hardness, friability, and DT were generated using Design-Expert® software (v. 11.1.2.0) (Stat-Ease, Inc., Minneapolis, MN, USA). ANOVA results for a quadratic model were reported for each response, along with coefficients based on the actual values. Correlation plots showing the relationship between predicted values and actual values, including the coefficient of determination ($R^2$), were presented. Additionally, plots depicting the relationship between internally studentized

residuals and run numbers were included, as well as normal plots of residuals. Design spaces were created for different compressional forces, where tablet hardness ranged from 5 to 9 kP, friability was limited to 0.2% or less, and DT fell between 3 and 7 min. For the verification step, a condition within the design space was selected, and the tablet properties obtained from this condition were compared to the predicted values, with the resulting percentage error calculated.

**Table 1.** Factors and responses of the Box–Behnken design.

| Formulas | Factors | | | Responses | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Thickness | | | Hardness | | |
| | Force (psi) | CCS (%) | MCC (%) | Actual (mm) | Predicted (mm) | Error (%) * | Actual (kP) | Predicted (kP) | Error (%) * |
| 1 | 1500 | 1 | 37 | 2.09 ± 0.02 | 2.09 | 0.00 | 4.92 ± 0.15 | 5.18 | −5.28 |
| 2 | 2500 | 1 | 37 | 1.95 ± 0.02 | 1.95 | 0.00 | 8.43 ± 0.17 | 8.63 | −2.37 |
| 3 | 1500 | 3 | 37 | 2.08 ± 0.03 | 2.08 | 0.00 | 5.31 ± 0.32 | 5.11 | 3.77 |
| 4 | 2500 | 3 | 37 | 1.96 ± 0.02 | 1.96 | 0.00 | 9.52 ± 0.27 | 9.26 | 2.73 |
| 5 | 1500 | 2 | 32 | 2.04 ± 0.02 | 2.04 | 0.00 | 4.61 ± 0.19 | 4.69 | −1.74 |
| 6 | 2500 | 2 | 32 | 1.90 ± 0.02 | 1.90 | 0.00 | 7.98 ± 0.32 | 8.12 | −1.75 |
| 7 | 1500 | 2 | 42 | 2.07 ± 0.02 | 2.07 | 0.00 | 5.78 ± 0.33 | 5.64 | 2.42 |
| 8 | 2500 | 2 | 42 | 1.95 ± 0.01 | 1.95 | 0.00 | 9.90 ± 0.25 | 9.82 | 0.81 |
| 9 | 2000 | 1 | 32 | 1.96 ± 0.01 | 1.97 | −0.51 | 6.24 ± 0.32 | 5.90 | 5.45 |
| 10 | 2000 | 3 | 32 | 1.97 ± 0.01 | 1.97 | 0.00 | 6.03 ± 0.32 | 6.15 | −1.99 |
| 11 | 2000 | 1 | 42 | 2.01 ± 0.02 | 2.01 | 0.00 | 7.31 ± 0.27 | 7.19 | 1.64 |
| 12 | 2000 | 3 | 42 | 2.03 ± 0.02 | 2.02 | 0.49 | 7.16 ± 0.09 | 7.50 | −4.75 |
| 13 | 2000 | 2 | 37 | 1.97 ± 0.01 | 1.97 | 0.00 | 7.37 ± 0.22 | 7.39 | −0.27 |
| 14 | 2000 | 2 | 37 | 1.98 ± 0.01 | 1.97 | 0.51 | 7.15 ± 0.33 | 7.39 | −3.36 |
| 15 | 2000 | 2 | 37 | 1.97 ± 0.01 | 1.97 | 0.00 | 7.32 ± 0.33 | 7.39 | −0.96 |
| 16 | 2000 | 2 | 37 | 1.95 ± 0.02 | 1.97 | −1.03 | 7.69 ± 0.33 | 7.39 | 3.90 |
| 17 | 2000 | 2 | 37 | 1.97 ± 0.01 | 1.97 | 0.00 | 7.44 ± 0.15 | 7.39 | 0.67 |

| Formulas | Factors | | | Responses | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Friability | | | DT | | |
| | Force (psi) | CCS (%) | MCC (%) | Actual (%) | Predicted (%) | Error (%) * | Actual (min) | Predicted (min) | Error (%) * |
| 1 | 1500 | 1 | 37 | 0.18 ± 0.02 | 0.18 | 0.00 | 2.51 ± 0.51 | 3.11 | −23.90 |
| 2 | 2500 | 1 | 37 | 0.11 ± 0.02 | 0.13 | −18.18 | 9.54 ± 0.35 | 9.76 | −2.31 |
| 3 | 1500 | 3 | 37 | 0.27 ± 0.02 | 0.25 | 7.41 | 1.13 ± 0.29 | 0.91 | 19.47 |
| 4 | 2500 | 3 | 37 | 0.07 ± 0.01 | 0.07 | 0.00 | 5.97 ± 0.45 | 5.37 | 10.05 |
| 5 | 1500 | 2 | 32 | 0.26 ± 0.03 | 0.27 | −3.85 | 1.31 ± 0.41 | 1.40 | −6.87 |
| 6 | 2500 | 2 | 32 | 0.16 ± 0.02 | 0.14 | 12.50 | 6.75 ± 0.32 | 7.22 | −6.96 |
| 7 | 1500 | 2 | 42 | 0.17 ± 0.07 | 0.19 | −11.76 | 3.37 ± 0.28 | 2.90 | 13.95 |
| 8 | 2500 | 2 | 42 | 0.11 ± 0.04 | 0.10 | 9.09 | 8.27 ± 0.13 | 8.18 | 1.09 |
| 9 | 2000 | 1 | 32 | 0.16 ± 0.02 | 0.16 | 0.00 | 8.04 ± 0.13 | 7.35 | 8.58 |
| 10 | 2000 | 3 | 32 | 0.22 ± 0.01 | 0.24 | −9.09 | 3.29 ± 0.27 | 3.42 | −3.95 |
| 11 | 2000 | 1 | 42 | 0.19 ±0.02 | 0.17 | 10.53 | 8.06 ± 0.48 | 7.93 | 1.61 |
| 12 | 2000 | 3 | 42 | 0.10 ± 0.03 | 0.10 | 0.00 | 4.59 ± 0.29 | 5.28 | −15.03 |
| 13 | 2000 | 2 | 37 | 0.12 ± 0.04 | 0.11 | 8.33 | 5.30 ± 0.37 | 6.10 | −15.09 |
| 14 | 2000 | 2 | 37 | 0.14 ± 0.03 | 0.11 | 21.43 | 5.59 ± 0.60 | 6.10 | −9.12 |
| 15 | 2000 | 2 | 37 | 0.08 ± 0.03 | 0.11 | −37.50 | 7.17 ± 0.31 | 6.10 | 14.92 |
| 16 | 2000 | 2 | 37 | 0.07 ± 0.00 | 0.11 | −57.14 | 6.75 ± 0.41 | 6.10 | 9.63 |
| 17 | 2000 | 2 | 37 | 0.13 ± 0.01 | 0.11 | 15.38 | 5.67 ± 0.51 | 6.10 | −7.58 |

* Error = (actual value − predicted value) × 100/actual value.

### *2.4. Evaluation of Black Pepper Extract Tablet Properties*

#### 2.4.1. Weight and Weight Variation

Twenty tablets were individually weighed using an analytical balance (Entris224i-1S, Sartorius AG, Otto-Brenner-Straße, Göttingen, Germany). The average value and standard deviation (SD) were reported. Equation (1) was used to compare the difference between individual weight and average weight to determine weight variation.

$$\text{Weight variation}(\%) = \left(\frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}}\right) \times 100 \quad (1)$$

#### 2.4.2. Thickness and Diameter

Twenty tablets were measured in thickness and diameter using a digital thickness gauge. The average value and SD were reported.

#### 2.4.3. Hardness

Ten tablets were measured hardness by a hardness tester (TBH 220 TD, Erweka GmbH, Otto-straße, Heusenstamm, Germany). The average value and SD were reported.

#### 2.4.4. Friability

Eleven tablets were dust removed using a soft brush and weighed using an analytical balance ($W_1$). Friability was tested using a friability tester (Model: CS-2, Tianjin Guoming Medicinal Equipment Co., Ltd., Hua Yuan, Tianjin, China). The drum of the friability tester was rotated at the rate of 25 rpm for 4 min. Then, the tablets were removed from the drum, dust removed, and weighed again ($W_2$). The friability was calculated using Equation (2).

$$\text{Friability}(\%) = \left(\frac{W_1 - W_2}{W_1}\right) \times 100 \quad (2)$$

#### 2.4.5. Disintegration Time

Six tablets were evaluated using a disintegration tester (Model: BJ-2, Tianjin Guoming Medicinal Equipment Co., Ltd., Hua Yuan, Tianjin, China). Water was used as a medium with temperature controlled at 37 ± 0.5 °C. The average values and SD were reported.

### *2.5. Analysis of Piperine Content*

Piperine was selected as a marker of black pepper extract. It was analyzed by high-performance liquid chromatography (Agilent 1260 Infinity, Agilent Technologies, Inc., Santa Clara, CA, USA). Ten black pepper extract tablets obtained from the optimal condition were pulverized using a mortar and pestle. It was accurately weighed for 200 mg ($n$ = 3) into a 100-mL volumetric flask before adding methanol and ultrasonicated for 10 min. Methanol was adjusted to the volume and mixed. Then, they were filtered using a nylon syringe filter (0.45 μm) and analyzed by the HPLC instrument.

Analysis was done on the InfinityLab Poroshell 120 EC-C18 column (150 × 4.6 mm, internal diameter, 4 μm) (Agilent Technologies, Inc., Santa Clara, CA, USA). The column temperature was controlled at 25 °C. The mobile phase of isocratic elution was composed of ultrapure water and methanol in a ratio of 30:70 $v/v$. The mobile phase flow rate was 1 mL/min. The injection volume was 10 μL. It was detected by a photodiode array detector at 340 nm. The total run time for each injection was 7 min with a retention time of piperine of approximately 4.9 min.

### *2.6. Statistical Analysis*

The difference between more than two groups was analyzed using a one-way analysis of variance (one-way ANOVA) followed by Tukey's HSD post hoc analysis using SPSS Statistics 22.0 (IBM, Madison Avenue, NY, USA). Data were significantly different when the $p$-value was less than 0.05 at a 95% confidence interval.

## 3. Results and Discussion

### 3.1. Impact of Factors on Black Pepper Extract Tablet Properties Obtained from Screening Step by OFAT Technique

The screening of factor levels was conducted using the OFAT technique. Figure 1 presents the physical properties, namely, thickness, hardness, friability, and DT, of black pepper extract tablets when the factor levels were altered. In Figure 1a, the impact of compressional force on the tablet properties is depicted. A formulation containing no disintegrant CCS with 42% MCC was prepared. Increasing the compressional force from 1000 to 2500 psi resulted in a thinner tablet, with tablet thickness significantly decreasing from 2.20 to 1.96 mm (with a tablet diameter of 12.7 mm). However, there was no significant difference observed between compressional forces of 2000 and 2500 psi. Tablet hardness significantly increased from 3.30 to 8.27 kP. The friability of the tablet decreased as the compressional force increased. The compressional force of 1000 psi yielded the highest friability (0.39%), but it remained within the acceptable range of not more than 1.0%. Increasing the compressional force from 1500 to 2500 psi did not significantly affect the friability value. DT significantly increased from 1.84 to 22.07 min when the compressional force increased from 1000 to 2000 psi. However, there was no significant difference in DT between tablets compressed using 2000 and 2500 psi. Considering the high hardness and low friability, a compressional force of 2000 psi was selected for further screening steps. Since the absence of a disintegrant resulted in a long DT, the next step involved varying the CCS content while keeping MCC at 42%. Figure 1b illustrates the impact of CCS on the tablet properties, ranging from 0 to 4%. Tablet thickness showed slight variations, ranging from 1.97 to 2.01 mm. Tablet hardness ranged from 6.87 to 7.80 kP, with no significant differences observed as CCS content increased. The friability value remained relatively unchanged, ranging from 0.14 to 0.17%, as CCS content increased. However, increasing the CCS content significantly shortened the DT from 22.07 to 2.83 min. A CCS content of 2% was selected for further screening steps due to its ability to provide a suitable DT that was neither too short (less than 3 min) nor excessively long (more than 30 min), surpassing the acceptable range. Figure 1c demonstrates the impact of MCC on the tablet properties. As MCC increased, tablet thickness also increased from 1.94 to 1.99 mm. There was no significant difference in hardness when comparing MCC contents of 27% and 32%. However, increasing MCC from 32% to 42% resulted in a significant increase in hardness from 5.88 to 7.80 kP. The friability and DT values did not significantly differ between formulations containing 27% vs. 32% MCC and 37% vs. 42% MCC. However, when comparing formulations with 27% and 32% MCC to those with 37% and 42% MCC, both the friability and DT were significantly different. In summary, a higher MCC content led to lower friability and prolonged DT.

Based on the screening of factor levels using the OFAT technique, it was found that the major factor impacting various tablet properties was the compressional force [19,20]. Increasing the compressional force resulted in decreased tablet thickness and increased tensile strength [21]. Furthermore, increasing the compressional force could prolong the DT of fast-disintegrating tablets containing aspirin [22]. Previous studies have shown similar results (Figure 1a) to the current work, where increasing the compressional force from 500 to 1500 psi decreased tablet thickness and friability, while increasing tablet hardness and prolonging the DT of *Thunbergia laurifolia* Lindl. leaf tablets [23].

CCS is a well-known tablet disintegrant that exhibits swelling properties when in contact with water, swelling to 4–8 times its original volume [24]. Its fluid uptake and swellability characteristics make it an effective superdisintegrant [25]. However, increasing CCS levels beyond 5% can prolong the DT due to the formation of a viscous gel layer that acts as a barrier to tablet disintegration [25]. In some cases, the use of CCS exceeding approximately 7.5% has been reported to prolong the DT of rapidly disintegrating tablets containing aspirin, ibuprofen, and ascorbic acid [22]. Although sodium starch glycolate (SSG) is commonly used as a disintegrant due to its good swelling and water uptake properties compared to CCS [26], CCS was found to be superior to SSG in terms

of shortening the DT [27]. In this work, CCS had the main impact on DT compared to other properties (Figure 1b), while the other properties were not significantly affected by CCS. These properties facilitate the easy development of the tablet formulation in terms of achieving a shortened DT with minimal impact on other tablet properties such as thickness, hardness, and friability.

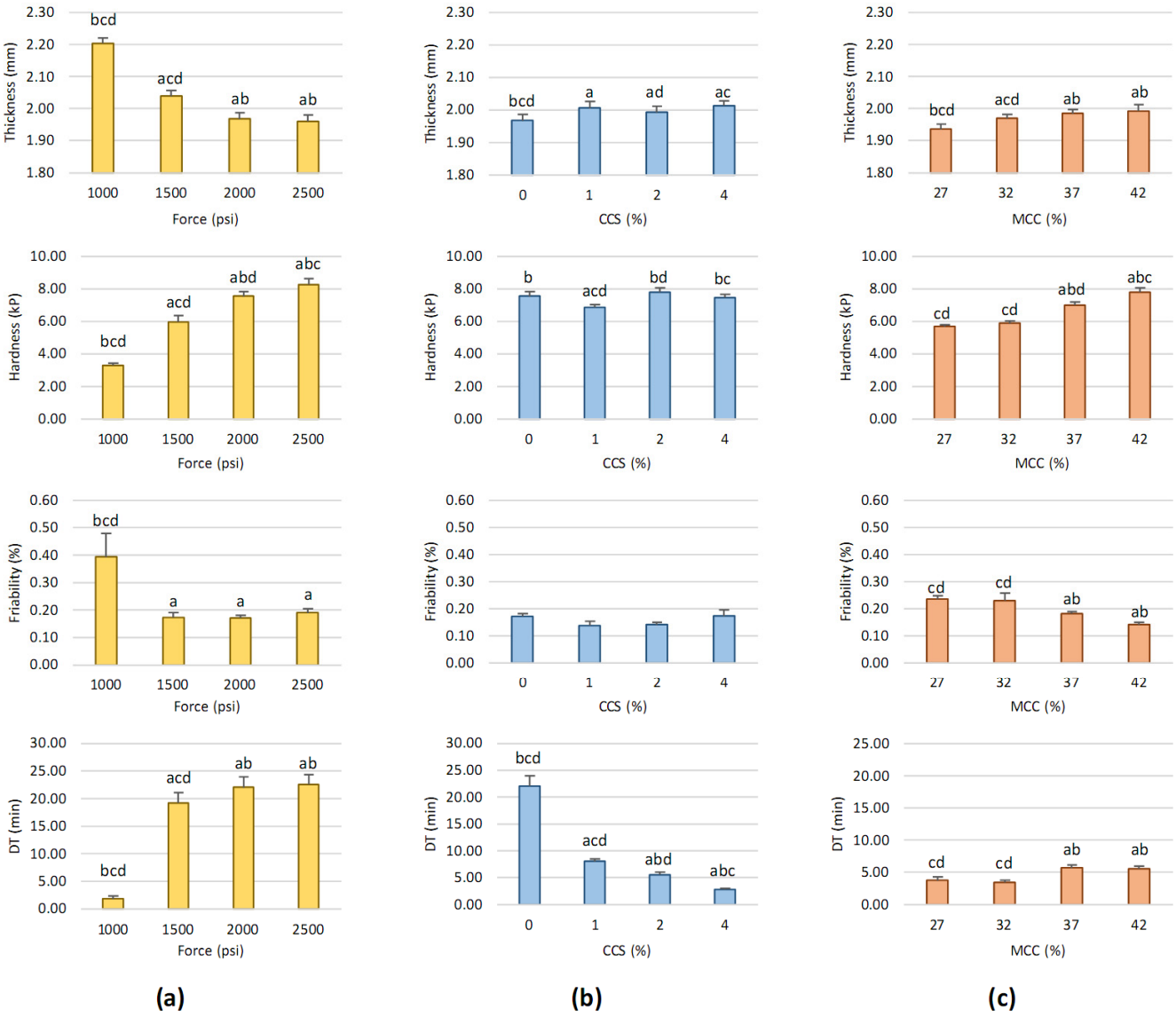


**Figure 1.** Physical properties, i.e., thickness, hardness, friability, and DT of black pepper extract tablets when (**a**) compressional force, (**b**) CCS, and (**c**) MCC were varied based on the OFAT technique. The symbols a, b, c, and d represented significant values ($p$-value < 0.05) compared with other levels.

MCC is the most commonly used tablet diluent and serves several functions, including being a directly compressible diluent, disintegrant, binder, lubricant, and glidant [28]. In this work, MCC was used as a diluent and binder to increase tablet hardness. Increasing MCC content resulted in decreased friability due to the increased hardness. However, the friability of the formulation in this work did not need to be further reduced, as it already exhibited low friability despite the application of low compressional force and the use of low MCC content (Figure 1c). The plasticity of MCC, along with its high surface area, high hygroscopicity, and comparatively low bulk density, accounts for its unique binding properties [29]. MCC has high compactibility at low pressure but poor flow characteristics [30]. To improve powder flowability, dibasic calcium phosphate, a free-

flowing material with no disintegration-enhancing properties, was used. Thus, a mixture of MCC and dibasic calcium phosphate was used as tablet diluents. The high porosity of MCC is thought to contribute to tablet swelling and disintegration, which occurs either through water entering the hydrophilic tablet matrix via capillary action in the pores or through the breakdown of hydrogen bonds. Additionally, MCC has a quick water-wicking rate and exhibits less elastic deformation, enabling tablet breakdown [28]. Although MCC exhibited disintegration properties, however, it increased tablet hardness and appeared to slightly prolong the DT (Figure 1c).

### *3.2. Impact of Factors on Black Pepper Extract Tablet Properties Obtained from Box–Behnken Design*

Following the screening step using the OFAT technique, the impact of factors on the tablet characteristics of black pepper extract was further examined using a DOE approach, specifically, the Box–Behnken design. A suitable range for each factor was selected based on the screening data. In addition to describing the linear effect of each factor, as done in the previous section using the OFAT technique, DOE also allowed for the identification of factor interactions and the characterization of the response surface [17,18]. By employing computer software, DOE was able to provide a comprehensive analysis of the linear, interaction, and quadratic effects, allowing for a more in-depth understanding of the complex impact of the factors compared to the OFAT screening method.

Plots comparing the predicted and actual values, along with their corresponding $R^2$ values, are presented in Figure 2. It can be observed that all responses achieved relatively high $R^2$ values, indicating a strong correlation between the predicted and actual values. Additionally, the plots depicting internally studentized residuals against run numbers for each response exhibited a desirable random scatter pattern, with all data points falling within the red border lines. Furthermore, the normal plots of residuals for each response displayed a straight-line pattern. These findings suggest that the residual analysis data was favorable. The data provided in Table 1 and Figure 2 collectively support the precision, reliability, and stability of the predictions [31–33].

The responses of tablet properties obtained from the Box–Behnken design are presented in Table 1. The actual values were compared with the predicted values obtained from the computer software and expressed as percent error. The percent errors for most responses were low, especially for tablet thickness and hardness, indicating the precision of the computer software. However, the percent error for tablet friability appeared to be high for some formulas. This can be explained by the calculation of a small friability value, which can result in a high percentage difference. For example, in Formula 16, the actual value of 0.07% was close to the predicted value of 0.11%, but the percent error seemed high at −57.14%.

The response surfaces of tablet thickness, hardness, friability, and DT, with varying compressional force, are shown in Figure 3. The ANOVA results for the quadratic model of black pepper extract tablet properties are presented in Table 2. Figure 3a demonstrates that decreasing tablet thickness was achieved by increasing the compressional force; the tablet became significantly thinner as the compressional force increased. Changing CCS content did not have a significant impact on tablet thickness. However, increasing MCC content significantly increased tablet thickness. Figure 3b displays that increasing the compressional force resulted in increased tablet hardness. The tablets became significantly harder as the compressional force increased. Changing CCS content did not significantly affect tablet hardness, whereas increasing MCC content significantly increased tablet hardness. Figure 3c shows that decreasing tablet friability was achieved by increasing the compressional force; the tablet became significantly less friable as the compressional force increased. Changing CCS content did not have a significant effect on tablet friability, while increasing MCC content significantly decreased tablet friability. Figure 3d demonstrates that shortening DT was achieved by decreasing the compressional force; the tablet had a significantly shorter DT as the compressional force decreased. Increasing CCS content significantly shortened DT. On the other hand, changing MCC content did not have a

significant effect on DT. It is worth noting that while MCC can function as both a tablet disintegrant and binder/diluent, the content of MCC acting as a disintegrant is typically lower compared to that acting as a binder/diluent, with ranges of 5–15% and 20–90%, respectively [24]. In this study, MCC was used at 32–42% and primarily played the role of a binder rather than a disintegrant. Therefore, increasing its content did not act as a disintegrant to shorten DT.

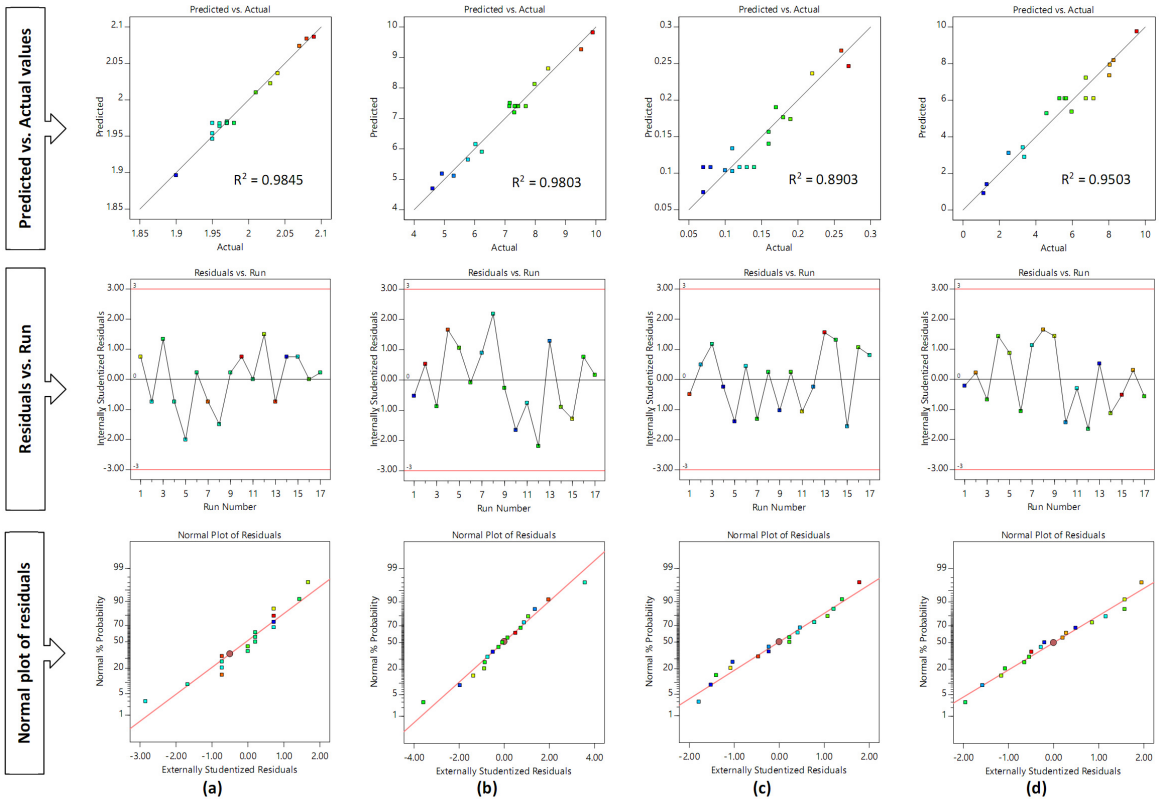


**Figure 2.** Plots between the predicted values vs. actual values with a coefficient of determination ($R^2$) (upper), the internally studentized residuals vs. run number (middle), and the normal % probability vs. externally studentized residuals (bottom) of (**a**) thickness, (**b**) hardness, (**c**) friability, and (**d**) DT of black pepper extract tablets.

**Table 2.** ANOVA for the quadratic model of thickness, hardness, friability, and DT of black pepper extract tablets.

| Source | | Thickness | | Hardness | | Friability | | DT | |
|---|---|---|---|---|---|---|---|---|---|
| | | Coefficient [a] | *p*-Value | Coefficient [a] | *p*-Value | Coefficient [a] | *p*-Value | Coefficient [a] | *p*-Value |
| Model | | - | <0.0001 * | - | < 0.0001 * | - | 0.0119 * | - | 0.0009 * |
| Intercept | | 1.9680 | - | 7.3940 | - | 0.1080 | - | 6.0960 | - |
| Linear | $X_1$-Force | −0.0650 | <0.0001 * | 1.9013 | <0.0001 * | −0.0538 | 0.0016 * | 2.7763 | <0.0001 * |
| | $X_2$-CCS | 0.0038 | 0.3257 | 0.1400 | 0.2458 | 0.0025 | 0.8232 | −1.6463 | 0.0009 * |
| | $X_3$-MCC | 0.0238 | 0.0003 * | 0.6613 | 0.0006 * | −0.0288 | 0.0321 * | 0.6125 | 0.0776 |
| Interaction | $X_1X_2$ | 0.0050 | 0.3522 | 0.1750 | 0.2998 | −0.0325 | 0.0704 | −0.5475 | 0.2328 |
| | $X_1X_3$ | 0.0050 | 0.3522 | 0.1875 | 0.2693 | 0.0100 | 0.5327 | −0.1350 | 0.7568 |
| | $X_2X_3$ | 0.0025 | 0.6336 | 0.0150 | 0.9262 | −0.0375 | 0.0434 * | 0.3200 | 0.4702 |
| Quadratic | $X_1^2$ | 0.0248 | 0.0015 * | 0.0168 | 0.9155 | 0.0285 | 0.0966 | −1.1893 | 0.0226 * |
| | $X_2^2$ | 0.0273 | 0.0008 * | −0.3658 | 0.0474 * | 0.0210 | 0.2004 | −0.1193 | 0.7788 |
| | $X_3^2$ | −0.0028 | 0.5915 | −0.3433 | 0.0589 | 0.0385 | 0.0359 * | 0.01825 | 0.9656 |
| Lack of Fit | | - | 0.6356 | - | 0.0890 | - | 0.5143 | - | 0.4341 |

A superscript (a) denotes coefficient values that were based on the coded equation. An asterisk (*) denotes significant values.

The impact of each factor (or linear effect) was found to be comparable to the results obtained from the OFAT. The mechanism of each factor was already discussed in the previous section, and this section provides additional information on the impact of factor interactions and quadratic effects. In addition to indicating the significance of linear effects, the ANOVA data also reveal the influence of factor interactions and quadratic effects. Table 2 shows that the interaction between CCS and MCC has a significant effect on decreasing tablet friability. The quadratic effect of compressional force significantly increases tablet thickness while also shortening DT. The quadratic effect of CCS significantly increases tablet thickness while decreasing tablet hardness. Furthermore, the quadratic effect of MCC significantly increases tablet friability. It is worth noting that the Lack of Fit for all responses was not significant, indicating that the model adequately fits the data.

Similar to previous studies that optimize herbal tablet formulations using the DOE approach, it was observed that compressional force is a major factor influencing tablet properties. Increasing the compressional force resulted in decreased tablet thickness and friability, while increasing tablet hardness and prolonging DT in various herbal tablet formulations such as Semha–Pinas effervescent tablets [34], Chatuphalathika extract tablets [35], and Prasakanphlu tablets [36]. The disintegrants CCS or SSG mostly shortened DT [36]. However, in the case of Chatuphalathika extract tablets, the DT was not affected by CCS because this specific tablet formulation easily disintegrated due to its characteristics, making CCS less important for such formulations [35]. Regarding the most commonly used diluent, MCC [37], it was found to increase tablet hardness and decrease friability, consistent with the findings of the present study.

The interaction between process and formulation factors that influence tablet properties has been explored in several studies [38–41]. However, demonstrating the mechanism of interaction between various factors can be challenging due to the complexity involved. The interactions between factors obtained through the DOE approach can be compared to the synergistic or antagonistic effects observed between certain factors or tablet excipients. For instance, combining excipients with different physical properties, such as brittle anhydrous dibasic calcium phosphate and ductile MCC, can be used to create directly compressible tablets of sitagliptin with desirable properties such as good mechanical strength (tensile strength over 2 $N/mm^2$), rapid disintegration (DT less than 2 min), and fast drug release [42]. The increase in CCS and MCC content demonstrated synergistic effects on the wetting ratio while exhibiting antagonistic effects on the wetting time. Additionally, a significant interaction effect between CCS and MCC was observed in relation to the wetting ratio, leading to increased water uptake [43]. In this case, the interaction effect of CCS and MCC could potentially influence DT. However, in the present study, it did not impact DT but resulted in decreased friability (Table 2). Exploring the mechanism behind this reduction in friability, which has not been previously reported, would be an interesting area for future investigation.

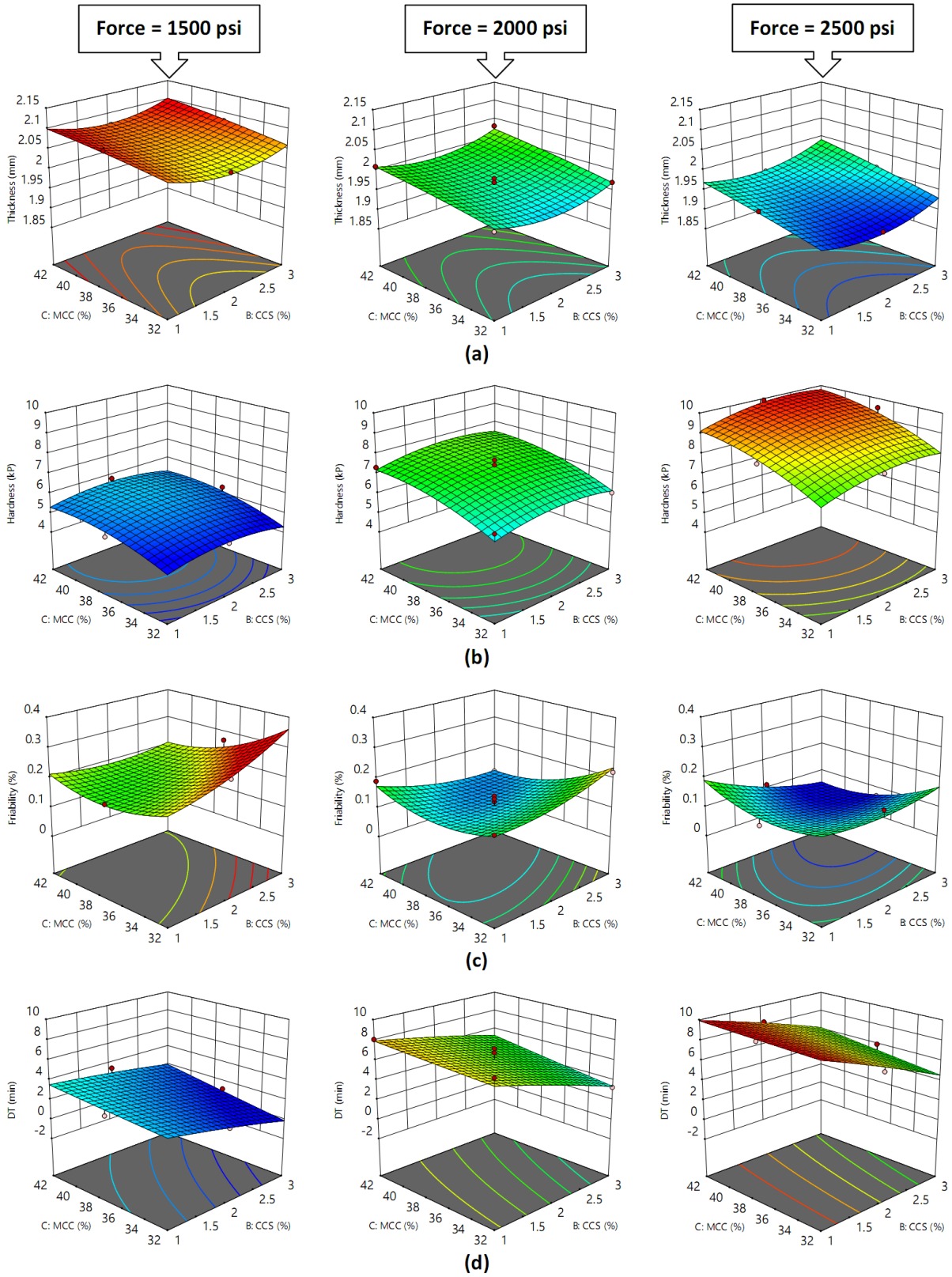


**Figure 3.** Response surfaces of (**a**) thickness, (**b**) hardness, (**c**) friability, and (**d**) DT of black pepper extract tablets obtained from the Box–Behnken design when different compressional forces were used. The colors red, green, and dark blue represent high, medium, and low values, respectively.

### *3.3. Design Spaces and Optimal Condition for Preparation of Black Pepper Extract Tablets*

The design spaces for black pepper extract tablets, where the tablets had a hardness of 5–9 kP, friability of not more than 0.2%, and a DT of 3–7 min when different compressional forces were applied, are presented in Figure 4. It was observed that a compressional force of 2000 psi provided the widest area of design space. Therefore, the verification point was selected from this compressional force to ensure the accuracy of the prediction. The optimal formulation was determined to be a compressional force of 2000 psi, CCS content of 2.2%, and MCC content of 37%. This optimal condition closely aligned with the typical range of CCS content, which is 0.5–5% (usually 2% for direct compression) for a disintegrant [24,44], and MCC content of 20–90% as a tablet diluent and binder [24].

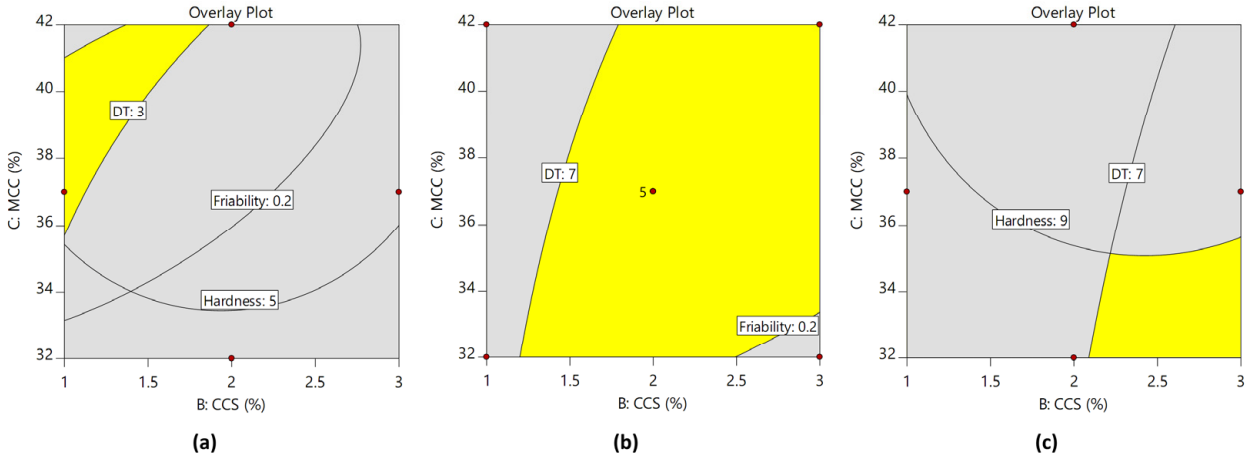


**Figure 4.** Design spaces (yellow area) that the black pepper extract tablets had a hardness of 5−9 kP, friability of not more than 0.2%, and DT of 3–7 min when different compressional forces were applied: (**a**) 1500 psi, (**b**) 2000 psi, and (**c**) 2500 psi.

The verified formulation exhibited a tablet weight of 198.39 ± 0.49 mg and a diameter of 9.67 ± 0.01 mm. The corresponding values for thickness, hardness, friability, and DT are presented in Table 3. It is noteworthy that no tablets demonstrated weight variation exceeding 7.5%, which falls within the acceptable range for a dietary supplement according to the United States Pharmacopeia. The percent errors between predicted and actual values for all parameters were less than 5%. Furthermore, all actual values fell within the lower and upper limits of the 95% confidence interval, as indicated in Table 3. These results collectively highlight the accuracy and reliability of the computer software's predictions [45].

**Table 3.** Verification data presented as predicted values, actual values, percent error, and lower to upper limit of 95% confidence interval.

| Responses | Predicted Values | Actual Values | Error (%) * | 95% CI (Lower to Upper) |
|---|---|---|---|---|
| Thickness (mm) ($n$ = 20) | 1.97 | 1.98 ± 0.02 | 0.51 | 1.94–2.00 |
| Hardness (kP) ($n$ = 10) | 7.41 | 7.36 ± 0.24 | −0.68 | 6.60–8.22 |
| Friability (%) ($n$ = 3, each 11) | 0.11 | 0.11 ± 0.02 | 0.00 | 0.03–0.19 |
| DT (min) ($n$ = 6) | 5.76 | 5.59 ± 0.39 | −3.04 | 3.59–7.93 |

* Error = (actual value − predicted value) × 100/actual value.

### *3.4. Piperine Content*

The optimal black pepper extract tablets contained 4.11 ± 0.05 mg of piperine, which falls within the permissible limit set by the Thai Food and Drug Administration, not exceeding 5 mg of piperine per day [46].

## 4. Conclusions

This study utilized the DOE approach to develop tablets containing black pepper extract. Through the conventional OFAT technique, appropriate levels of three factors—compressional force, CCS, and MCC—were identified. The Box–Behnken design was employed to determine the suitable levels of each factor. The results demonstrated that the tablet properties of black pepper extract were significantly influenced by the linear, interaction, and quadratic effects of these factors. The optimal formulation, consisting of a compressional force of 2000 psi, CCS of 2.2%, and MCC of 37%, exhibited desirable tablet characteristics. These tablets exhibited appropriate hardness, low friability, and a short DT. The accuracy of the computer software's predictions was evident from the very low percent error values. In summary, the application of the DOE approach led to the successful development of black pepper extract tablets. The DOE approach provided valuable insights into the impact of compressional force, CCS, and MCC on the tablet properties. These developed tablets can serve as food supplement products, offering the desired properties to consumers.

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